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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

Iversen et al.

SERIAL NO.: 09/493,427

FILED: January 29, 2000

FOR: ANTISENSE RESTENOSIS COMPOSITION AND METHOD

EXAMINER: J. Epps

ART UNIT: 1635

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dwight D. Weller, declare and affirm as follows:

I am currently employed as Senior Vice President of Chemistry and Manufacturing at AVI Biopharma Inc. I have been employed at AVI Biopharma, Inc,. previously known as Antivirals Inc., since 1992. Prior to that, I was Professor of Chemistry at Oregon State University, Corvallis, Oregon, USA from 1978 to 1992. I collaborated and consulted with Antivirals, Inc. from 1980 until 1992.

I received a Ph.D. in the field of Organic Chemistry from the University of California at Berkeley in 1976.

I am a co-inventor on the above-referenced application. The following facts describe a clinical trial carried out in support of the claimed invention, on behalf of AVI Biopharma, Inc.

AVI BioPharma, Inc. has completed a Phase II clinical study employing a phosphorodiamidate-linked morpholino oligomer (PMO)[1] targeting the start codon of c-myc mRNA, having SEQ ID NO: 1 (5'-ACGTT GAGGG GCATC GTCGC-3'), as disclosed and claimed in the above-referenced application, for prevention of restenosis following PTCA.

Patients enrolled in the study had existing recurrent restenosis following PTCA. The entry

[1] The PMO had phosphordiamidate intersubunit linkages as shown in pending claim 38, where X = $N(CH_3)_2$, Y = O, and Z = O.

criteria targeted patients with a high probability of restenosis, including patients that were CMV positive, diabetic and/or had prior stent placement.

The patients (33 total) were divided into three treatment groups, as described below. All underwent PTCA (percutaneous transluminal coronary angioplasty) followed by stent implantation. Groups A and B then were administered the oligomer, which was delivered locally to the treated area using an Infiltrator® delivery catheter balloon, provided by InterVentional Technologies (San Diego, California).

Group A received 3 mg of oligomer, a dose determined in preclinical pig studies to be sub-optimal and not expected to result in full therapeutic response.

Group B received 10 mg of oligomer, a dose determined in preclinical pig studies to be at or near the optimal therapeutic dose.

Group C received no oligomer, and did not undergo inflation of the delivery catheter balloon, due to the potential for added vessel injury. However, this group underwent the equivalent procedure for PTCA and follow-up stenting.

Six months following these procedures, MLD (maximum lumen diameter) and extent of restenosis were determined. The latter endpoint includes any vessel region with approximately 50% reduction in lumen area.

The data, as shown below, indicate evidence of efficacy in Group B (10 mg dose) as measured by both endpoints. No drug related serious adverse effects were observed.

Phase II Trial Interim Results (21/33 Evaluable Patients)

Group	A (PTCA/stent; 3 mg PMO via balloon catheter)	B (PTCA/stent; 10 mg PMO via balloon catheter)	C (PTCA/stent only)
Final lesion MLD	2.37 mm	2.83 mm	2.22 mm
Restenosis, Stent	66.7%	11.1%	40.0%

Enclosed, for comparative purposes, is a report (Kutryk *et al., J. Amer. Coll. Cardiology* 39:281-7, 2002) describing a clinical study ("the ITALICS study") employing an antisense phosphorothioate oligonucleotide targeted to the same region of c-myc mRNA, for inhibition of restenosis. This oligonucleotide is also disclosed in cited reference Zalewski *et al.*, U.S. Patent No. 6,133,242, as SEQ ID NO: 1 (5'-AACGT TGAGG GGCAT-3'). The report concludes that

this study failed to show evidence of efficacy (see e.g. Conclusions, p 281; Table 2, p 284).

The study, as described in the report, was done under conditions generally comparable to the AVI Biopharma study described above. The vessels were stented post-PCTA, and the same amount of oligomer (10 mg) was delivered, using a delivery catheter balloon for local intracoronary vessel delivery. The significant difference is that the ITALICS study used a phosphorothioate oligonucleotide, while the AVI Biopharma study used an uncharged morpholino oligomer. As described in the pending application, these oligomers exhibit efficient cell uptake and binding to mRNA (e.g. page 16, lines 10-16; page 14, line 26 to page 15, line 5).

In summary, the interim clinical results described herein demonstrate that the claimed method for reduction of restenosis in a human patient, employing administration of a morpholino oligomer having uncharged phosphorus-containing linkages, showed significant benefits relative to a method employing a phosphorothioate-linked oligonucleotide.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

30 April

Date